Plasmodium resistance

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West African Network for Clinical Trials of Antimalarial Drugs

L'AFRIQUE VICTIME D'UN TRAFIC DE FAUX MÉDICAMENTS

SURVEY OF THE QUALITY OF SELECTED ANTIMALARIAL MEDICINES CIRCULATING IN SIX COUNTRIES OF SUB-SAHARAN AFRICA

Figure 10:
Comparison of tablets appearance for two SP samples from the same manufac

The sample on the left does not contain pyrimethamine

Figure 11:
ACTs and SPs: Proportions of compliant, moderately non-compliant and extremely non-compliant* samples

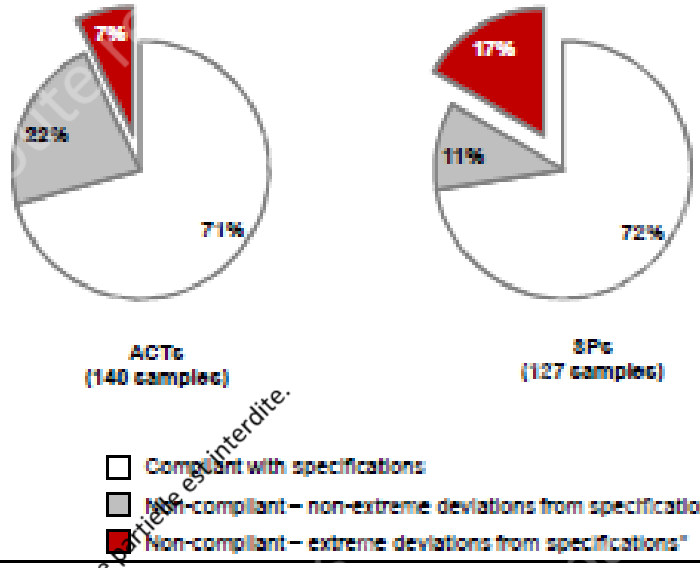


Table 19: Manufacturers of tested artemether/lumefantrine samples

Manufacturer	No. of samples tested	No. of batches tested	Countries of collection
Beijing Novartis Pharma Ltd, China / Novartis Pharmaceuticals Corporation, USA	64	40	Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania
Ajanta Pharma Ltd, India	10	6	Cameroon, Kenya
GVS Labs, India	6	4	Ghana, Nigeria
Jiangsu Yixing Forward Pharm. Factory, China	5	4	Nigeria
Addis pharmaceutical factory, Ethiopia	3	2	Ethiopia
Bliss GVS Pharma Ltd, India	3	1	Ghana
Ernest Chemists Ltd, Ernest, Ghana	3	2	Ghana
Naxpar Lab Ltd, India	3	2	Nigeria
Dandadams Pharmaceutical Industry Ltd, Ghana	2	1	Ghana
Ecomed Pharma Ltd, Nigeria	1	1	Nigeria
Ipca Laboratories Ltd, India	1	1	Kenya
Jayson Pharmaceuticals Ltd, Bangladesh	1	1	Ghana
Kinapharma Ltd, Ghana	1	1	Ghana
Macleods Pharmaceuticals Ltd, India	1	1	Nigeria
May & Baker Nigeria Plc, Nigeria	1	1	Nigeria
Medreich Plc, India	1	1	Ghana
Mekophar Chemical Pharm. Joint-Stock Company, Viet Nam	1	1	Nigeria
Universal Corporation Ltd, Kenya	1	1	Kenya

Quality Assurance and Safety: Medicines

Department of Essential Medicines and Pharmaceutical Policies

World Health Organization

Table 3.3. Associations between concentrations of antimalarial drugs on day 7 and therapeutic response

Drug	Therapeutic cut-off concentration (ng/ml)	Treatment failure rate (%) below vs above therapeutic concentration cut-off	Reference
Piperaquine	> 30	36 vs 6.8 ($p<0.001$)	(293)
Lumefantrine	> 280/500	49 (< 280) vs 6 (> 500)	(337)
	> 280	49 vs 25 (p value not reported)	(270)
	> 600	22 vs 0 ($p<0.001$)	(347)
	≥ 400	5.9 vs 0 ($p=0.001$)	(275)
	> 280	7.7 vs 1.4 ($p=0.027$)	(274)
	> 175	24 vs 1.1 ($p<0.001$)	(348)
	> 500	25 vs 6.5 ($p<0.01$)	(349)
Mefloquine	> 500	28 vs 0 ($p=0.0003$)	(350)
Desethylamodiaquine	> 75	25 vs 0 ($p=0.096$)	(247)
	> 16	44 vs ~22 (p value not reported)	(234)

Malaria gaps of knowledge

- Biology of parasite: growth regulation
- Transmission of parasite: vector capacitance
- Genome of parasite & mosquito: control of variability
- Induced immunity: efficient vaccine
- Physiopathology of disease: role of microbiote
- Mecanisme of drug resistance: ears of hippopotame

Fixed dose combinations

Artemether-lumefantrine	COARTEM, RIAMET	Novartis, Ajanta	2004
Artesunate-amodiaquine:	ASAQ, COARSUCAM	DNDi/Sanofi	2008
DHA-piperaquine:	EURARTESIM	Sigma-Tau	2011
Artesunate-mefloquine:	CIPLA tab	DNDi/Cipla Ltd	2012
Artesunate-pyronaridine:	PYRAMAX	Shin Poong Pharm	2012

ACT combination	Recommended dose	Treatment course
artemether/lumefantrine (AL)	1.4–4 mg/kg/dose 10–16 mg/kg/dose	Twice daily for three days
artesunate+/amodiaquine (AS+AQ, ASAQ)	2–10 mg/kg/day 7.5–15 mg/kg/day	Daily for three days
artesunate+/mefloquine (AS+MQ, ASMQ)	4 mg/kg/day (2–10 mg/kg/day) Total dose of 25 mg/kg	Daily for three days Divided daily for three days
artesunate+sulfadoxine-pyrimethamine (AS+SP)[a]	4 mg/kg/day (2–10 mg/kg/day) 25 mg/kg (S) (25–70 mg/kg (S))	Daily for three days Once on day-1
dihydroartemisinin+piperaquine (DHA PPQ)	4 mg/kg/day (2–10 mg/kg/day) 18 mg/kg/day (16–26 mg/kg/day)	Daily for three days

EDCTP

European and Developing Countries Clinical Trials Partnership

A Phase IIIb/IV comparative, randomised, multi-centre, open label, parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of new ACTs

Project Coordinator
Abdoulaye Djimde
MRTC, Bamako

West African Network for Clinical Trials of Antimalarial Drugs

Country	Study Sites	Test products	Comparator
Mali	Kolle	PA or DHA-PQP	AL
Mali	Bougoula-Hameau	PA or DHA-PQP	ASAQ
Burkina Faso	Banfora	PA or DHA-PQP	ASAQ
Burkina Faso	Bobo-Djoulasso	PA or DHA-PQP	AL
Guinea	Maferenya	PA or DHA-PQP	ASAQ

trial number: PACTR201105000286876

- pyronaridine-artesunate (PYRAMAX, Shin Poong-MMV)
- dihydroartemisinin-piperaquine (EURARTESIM, Sigma-Tau-MMV)
  - artemether-lumefantrine (COARTEM or COARTEM-D)
  - artesunate-amodiaquine (ASAQ Winthrop/Coarsucam)
- over a two-year period, children and adult uncomplicated malaria

West African Network for Clinical Trials of Antimalarial Drugs

Role of repeated doses

Treatment: 3 days per malaria episode

Treatment follow-up on Day 7, Day 14, Day 21, Day 28, Day 35, and Day 42

Study follow-up period of 2 years in children and adults

4710 patients: intent-to-treat population

4442 patients: Day 42 efficacy evaluable population

SP-C-013-11 (IP-07-31060-002)

Medicines for Malaria Venture
A nonprofit Foundation

SHIN POONG PHARM. CO., LTD.
SEOUL, KOREA

Sagara I, *et al.* Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a sub-study of the WANECAM randomised trial, Lancet Infect Dis. 2015 Oct 21.

Malaria resistance: facts and hypothesis

- **Facts**
  - ACTs show more than 90% efficiency
  - International guidelines
  - 5 different ACTs
  - Decreased sensitivity to artemisinin
  - Resistance to partner drugs
  - Molecular markers of resistance
- **Hypothesis**
  - Elimination and eradication?
  - Climate change will drive new transmission patterns?
  - Triple or more drug combination?
  - Really new drugs?
  - Vivax for ever?

Resistance to Artemisinin

Decelerated progression of parasite cycle

Reducing artemisinin activation by haem in ring stages

Increasing time to repair damaged proteins / cellular components

Reduces exposure of trophozoites to artemisinin

Increased dormancy

Subsequent exit quiescence when drug level decreased

Increased gamecytogenesis

Increase the probability of transmission

Resistance to Artemisinin: KELCH propeller Domain

Sensitive parasite:

Artemisinin is activated by haem produces in ring

Activated artemisinin alkylate nearby proteins : cell death

K13 binds to transcriptional factor avoiding antioxydant response

Resistant parasite:

K13 mutation : disrupt binding of transcriptional factor

Upregulation of antioxydant proteins (unfolded)

Increased capacity to repair proteins

Resistance to Artemisinin combination therapies

Conditions of emergence:

- Low transmission = low immunity
- Low transmission = more symptomatic = more drug
- Focal transmission (remote areas, forests, borders) = fake drugs
  uncontrolled treatment = repeated non-curative doses
- Fewer multiclonal infection = less competition

Conditions of spreading:

- Genetic backbone: fitness advantage

Optimizing drug use

Ring-stage survival assay (RSA) (in vitro)

K13 propeller (molecular) C580Y

- eastern Mekong (Cambodia, Laos, Viet Nam): C580Y, R539T, Y493H, I543T
- western Mekong (China, Myanmar, Thailand): F446L, N458Y, P574L, R561H

Markers for partner drugs

Parasitological failure: parasite on day 3

Clinical therapeutic failure: day 28 or 42 depending on partner drug

Multiple first line therapies

ISGlobal Barcelona Institute for Global Health

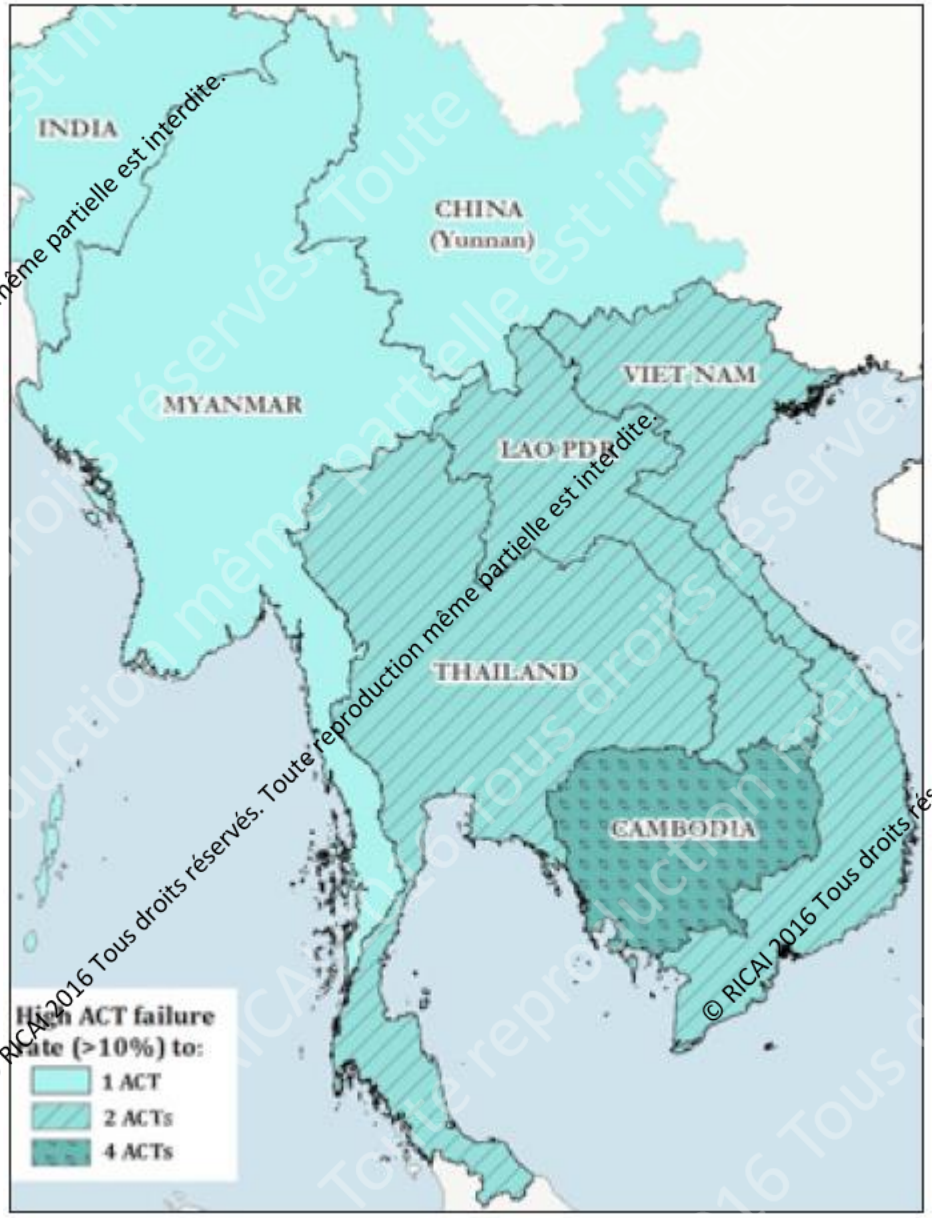
Bill & Melinda Gates foundation

MESA

Malaria Eradication Scientific Alliance

World Health Organization

Situation of ACT failures in the Greater Mekong subregion



Anticipating

Target product profile

SERCaP : Single encounter Radical Cure & Prophylaxis

Really new drugs

Mass drug administration

ISGlobal Barcelona Institute for Global Health

Bill & Melinda Gates foundation

MESA

Malaria Eradication Scientific Alliance

World Health Organization

Target product profile

TCP1: Capable of replacing fast-acting artemisinin

TCP2: Long duration combination partner

TCP 3a: Killing hypnozoites

TCP 3b: Transmission blocking

TCP4: Blocking liver infection by sporozoite

Killing liver schizontes

Single Encounter Radical Cure and Prophylaxis: SERCaP

Single dose

Prevention of transmission

Prevention of relapses

Post-treatment prophylaxis

Really New schizonticides: phase II

OZ439:	3rd generation endoperoxyde	Sanofi (-> 2018)
KAE609:	inhibitor sodium chanel PfATP4	Novartis
KAF156:	Imidazolopiperazine	
DSM265:	Inhibitor of dihydroxyorotate deshydrogenase (DHODH)	

Fast actives & actives against artemisinin resistant strains
Long half-life : over a week for a single dose

Partner drugs: 3 options

Piperaquine -> resistances already exist

New member of old family : ferroquine or Pyronaridine

Paired two new drugs

On going Trials: OZ439 + Piperaquine

OZ439 + Ferroquine

OZ439 + DSM265

KAE609 + ?

QUINOLAC (2008 –on going)

M. Medebielle - JB Bouillon - S Picot

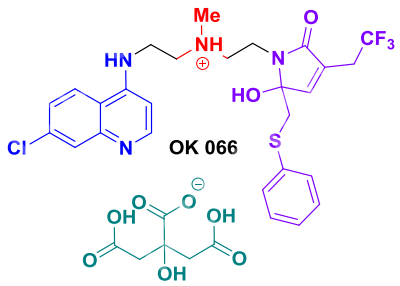
Original γ-hydroxy-γ-lactam scaffold

Hybrid with 4-amino-7-chloro quinoline & 8-amino-2-methoxy quinoline skeletons (*first and second generation*)

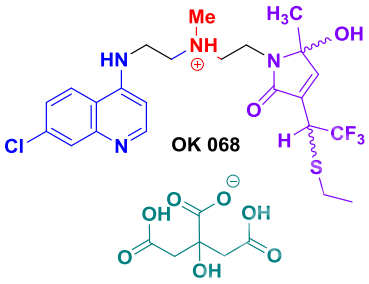
Structures without quinoline unit (*3rd generation*), Two series of **γ-hydroxy-γ-lactams** / 2 syntheses (7 steps vs 3 steps based on tetronic acid

15-300 nM (3D7, W2), no cytotoxicity (HUVEC cells), low resistance index, stable at pH 5,4 and 7,2 up to 72 h (LC/MS), ***but highly lipophilic***

- *J. Med. Chem*. **2013**, *56*, 73;
- *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6167;
- *Tetrahedron Lett*. **2013**, *54*, 4577;
- *Eur. J. Org. Chem*. **2015**, *28*, 6259;
- *Bioorg. Med. Chem. Lett*. **2016**, *26*, 5308;
- 1 patent.

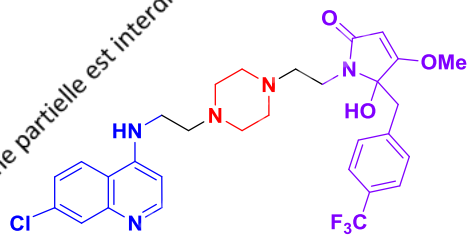


IC_{50} (3D7) = 26 nM
IC_{50} (W2) = 49 nM

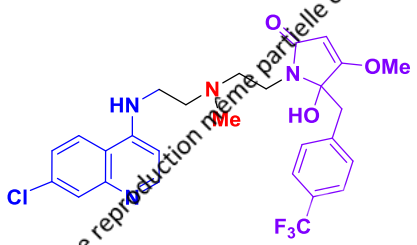


IC_{50} (3D7) = 19 nM
IC_{50} (W2) = 42 nM

First generation



IC_{50} (3D7) = 19 nM
IC_{50} (W2) = 17 nM



IC_{50} (3D7) = 14 nM
IC_{50} (W2) = 34 nM

Second generation

Third generation: no 4-aminQ skeleton
IC_{50} = 100-175 nM

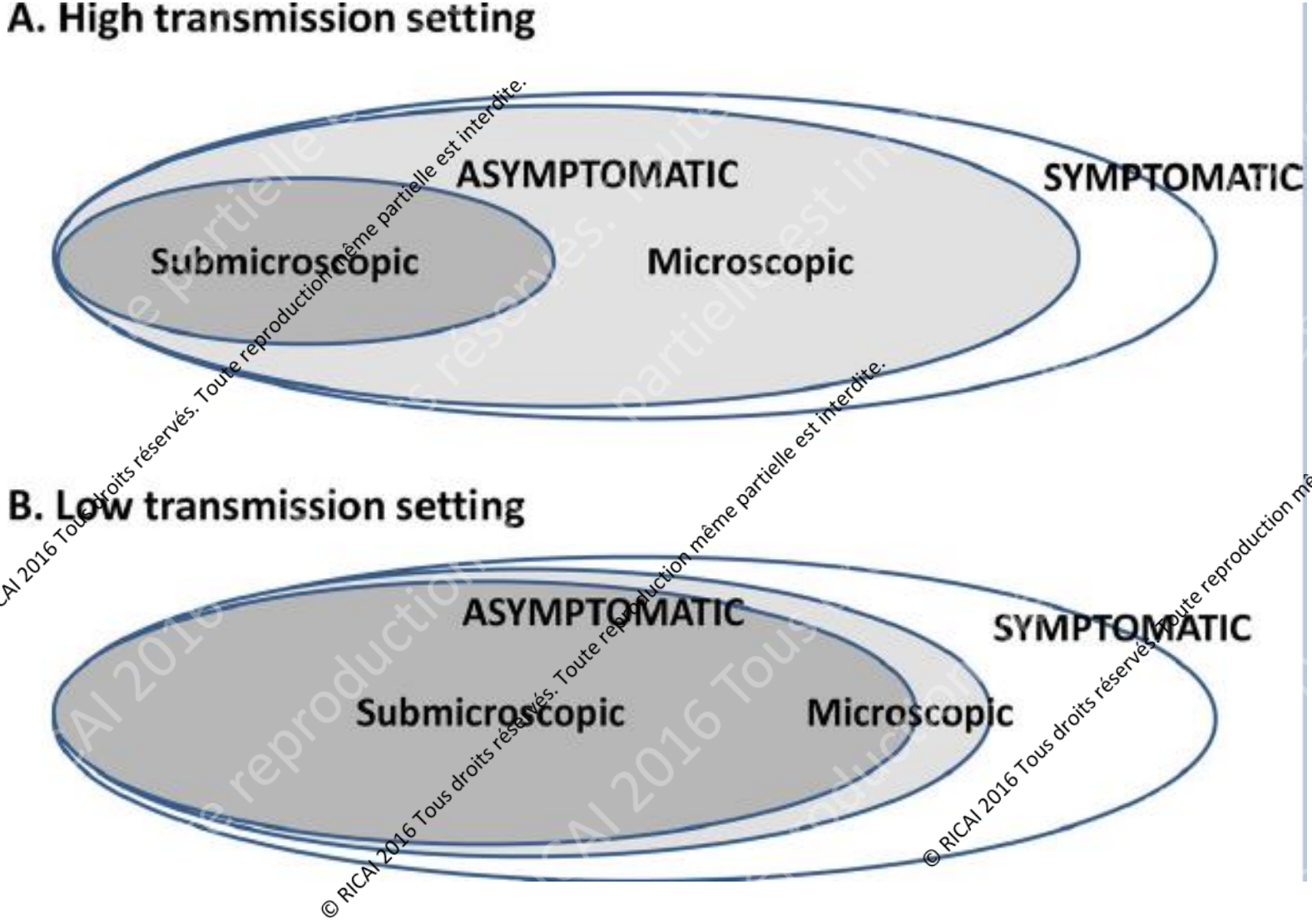
Mass drug administration: empiric

Aims:	Elimination in low-endemic areas
	Control of epidemics
Protocole:	Full treatment dose
	Repeated twice at monthly intervals
People:	Most recipients are healthy (no parasite)
	Some have asymptomatic malaria
Area:	Low seasonal transmission areas
Period:	Dry season
Drug:	Different from 1st line: DHA-P + single low dose PQ

Windows of resistance selection: 1 month after last dose

Surveillance and response

- Elimination stages
- Less than 1000 people at risk per year
- Hot pops / hot spots
- Reactive case detection (1-3-7)
  - Passive detected case (day 1)
  - Household, neighbors, contact : active detection and Treatment (day 3)
  - Appropriate public health response (day 7)



The role of submicroscopic malaria in malaria transmission: what is the evidence?

Jessica T. Lin[1], **David L. Saunders**[2], and **Steven R. Meshnick**[3]

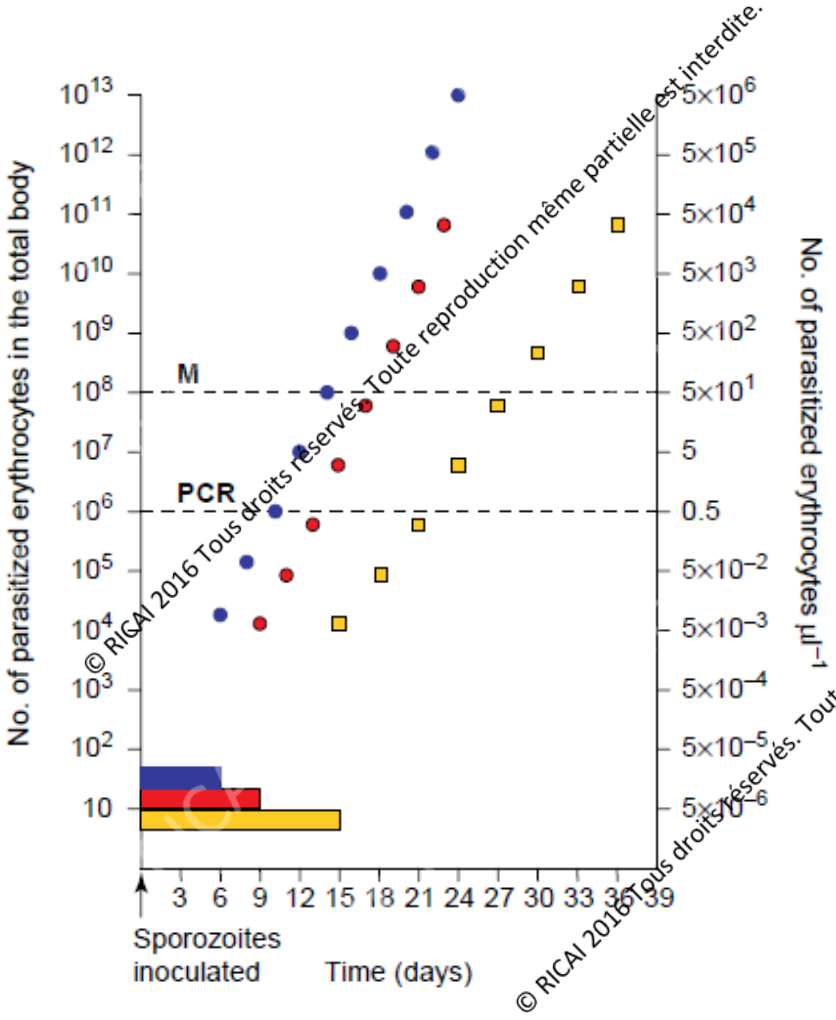
Parasite loads

Total body

- Liver stages : 10^3 to 10^5
- Asymptomatic malaria : 1 to 10^5
- Symptomatic malaria : 10^8 to 10^{12} (10 millions-100 milliards)
- Severe malaria : 10^9 to 10^{13}

Per µl of blood

- Liver stages : n.a.
- Asymptomatic malaria : 0 to 0.05
- Symptomatic malaria : 50 to 500.000
- Severe malaria : 500 to >5.000.000



TRENDS in Parasitology Vol.20 No.9 September 2004

Table 2. Limit of detection of a single infected red blood cell (5×10^6 RBC/µl; 8×10^3 WBC/µl)

iRBC/µL	Parasitemia	Microscopy	RDT-Antigen	Nucleic Acid	Hemozoin
50,000	1.00000000%	Average Microscopist >100 iRBC/µL Expert Microscopist ≥5–10 iRBC/µL	FIND Assay Performance 2000 to 200 iRBC/µL	18S rRNA mtDNA Stevor TARE-2 Whole Blood 5 to 0.5 iRBC/µL Concentrated Whole Blood 0.05 to 0.005 iRBC/µL	Magneto-Optical 10–40 iRBC/µL MDM Whole Blood 0.5 to 0.05 iRBC/µL
5,000	0.10000000%				
500	0.01000000%				
50	0.00100000%				
5	0.00010000%				
0.5	0.00001000%				
0.05	0.00000100%				
0.005	0.00000010%				
0.0005	0.00000001%				

Malaria diagnosis for malaria elimination

Peter A. Zimmerman and Rosalind E. Howes

Rolling-circle-enhanced enzyme activity detection (READ)

Droplet Microfluidics Platform for Highly Sensitive and Quantitative Detection of Malaria-Causing *Plasmodium* Parasites Based on Enzyme Activity Measurement

Sissel Juul,[†,▽] Christine J. F. Nielsen,[‡,▽] Rodrigo Labouriau,[‡,▽] Amit Roy,[‡] Cinzia Tesauro,[§] Pia W. Jensen,[‡] Charlotte Harmsen,[‡] Emil L. Kristoffersen,[‡] Ya-Ling Chiu,[†] Rikke Frøhlich,[‡] Paola Fiorani,[⊥] Janet Cox-Singh,[∥] David Tordrup,[‡] Jørn Koch,[#] Anne-Lise Bienvenu,[△] Alessandro Desideri,[§] Stephane Picot,[△] Eskild Petersen,[□] Kam W. Leong,[†] Yi-Ping Ho,[○] Magnus Stougaard,[#,○] and Birgitta R. Knudsen[‡,○,*]

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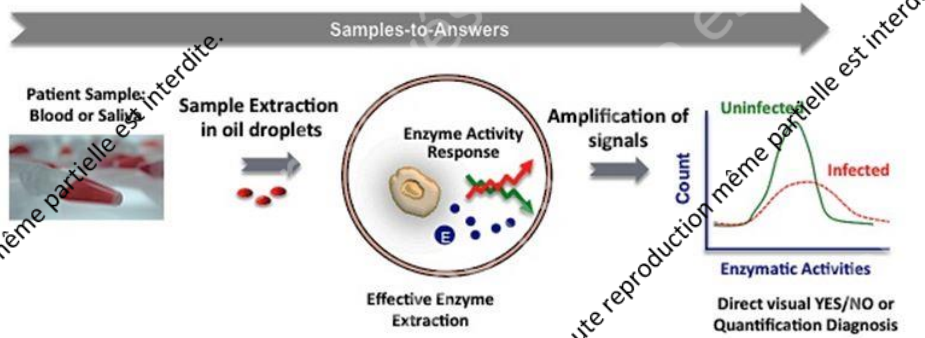
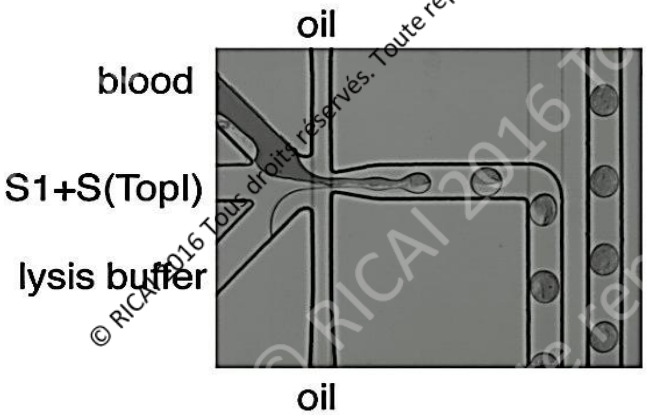
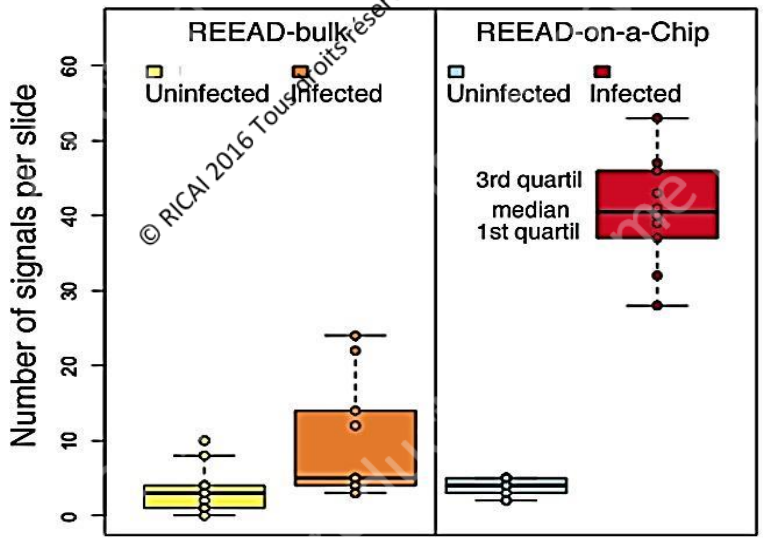






INSTITUT DE CHIMIE ET BIOCHIMIE MOLECULAIRES ET SUPRAMOLECULAIRES
icb ims UMR 5246

Loop-mediated Isothermal Amplification (LAMP)

Isothermal DNA amplification (Notomi T, Nucleic Acids Res. 2000.)

First application to malaria diagnosis : Poon LLM, Clin. Chem. 2006.

Suitable tool for diagnosis in endemic areas. Polley SD, J. Infect. Dis. 2013.

Illumigene Malaria plus(Meridian) Pos / Neg in 45 minutes

		Light microscopy +	Light microscopy -	
LAMP	+	40	3	PPV = 0.93
	-	0	37	NPV = 1
		Sensitivity = 1	Specificity = 0.925	

Non-inferiority of Loop-mediated Isothermal Amplification compared to light microscopy for screening patients with imported malaria in a non-endemic setting (submitted)

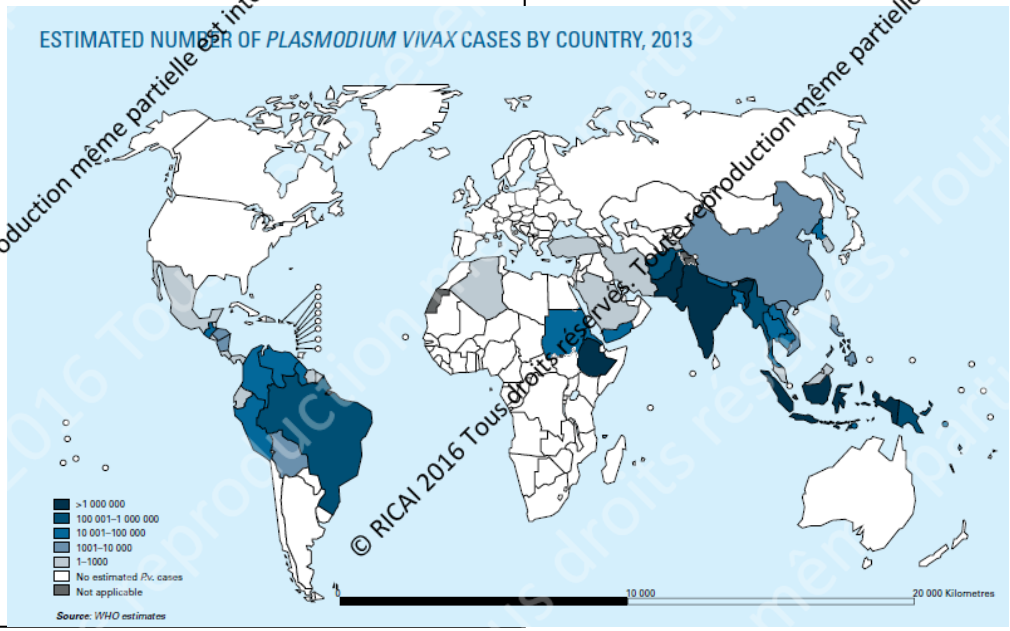
in vivax veritas, sed in hypnozoites sapientia

Plasmodium vivax best friends

Reticulocytes (no culture)

Hypnozoites (no cure)

Gametocytes (no elimination)



Malaria transmission in Northern Europe (speculative!)

- Complexity of transmission cycles
  - Ecological, Societal, Behavioral factors
  - Environmental changes: new wetlands, urban greenspace
  - Climate change: +2 +4 +6°C by 2100 ?
- Vectors
  - adaptation
  - spreading : tyres, trucks, highways
  - Importation versus establishment
  - UK anophelines are competent
- Models:
  - falciparum : probably not suitable
  - vivax 4 months/yr by 2030 in southeast England
  - vivax 4 months/yr by 2080 Southern Scotland!

Medlock & Leach, LID june 2015

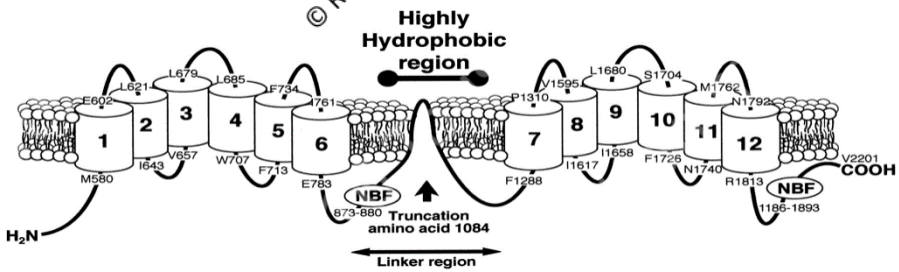
P. vivax resistance: prepare the war

- Therapeutic failures (India, Turkey, Indonesia, PNG, Thailand…)
- Prophylaxis failures
  - ATV-PG (Ethiopia, Povinelli 2003. SEA, Jimenez 2006)
  - MQ (French Guiana, Picot 2005)
- Decreased primaquine efficacy (Indonesia, PNG, Thailand…)

Identification of the *Plasmodium vivax mdr*-Like Gene (*pvmdr1*) and Analysis of Nucleotide Polymorphisms among Isolates from Different Areas of Endemicity

Sara Brega,[1] Benoit Meslin,[1] Frédérique de Monbrison,[1,2] Carlo Severini,[5] Luigi Gradoni,[5] Rachanee Udomsangpetch,[4] Inge Sutanto,[6] François Peyron,[1,3] and Stéphane Picot[1,2]

JID 2005:191 (15 January)



Eibach *et al. Malaria Journal* 2012, **11**:347
http://www.malariajournal.com/content/11/1/347

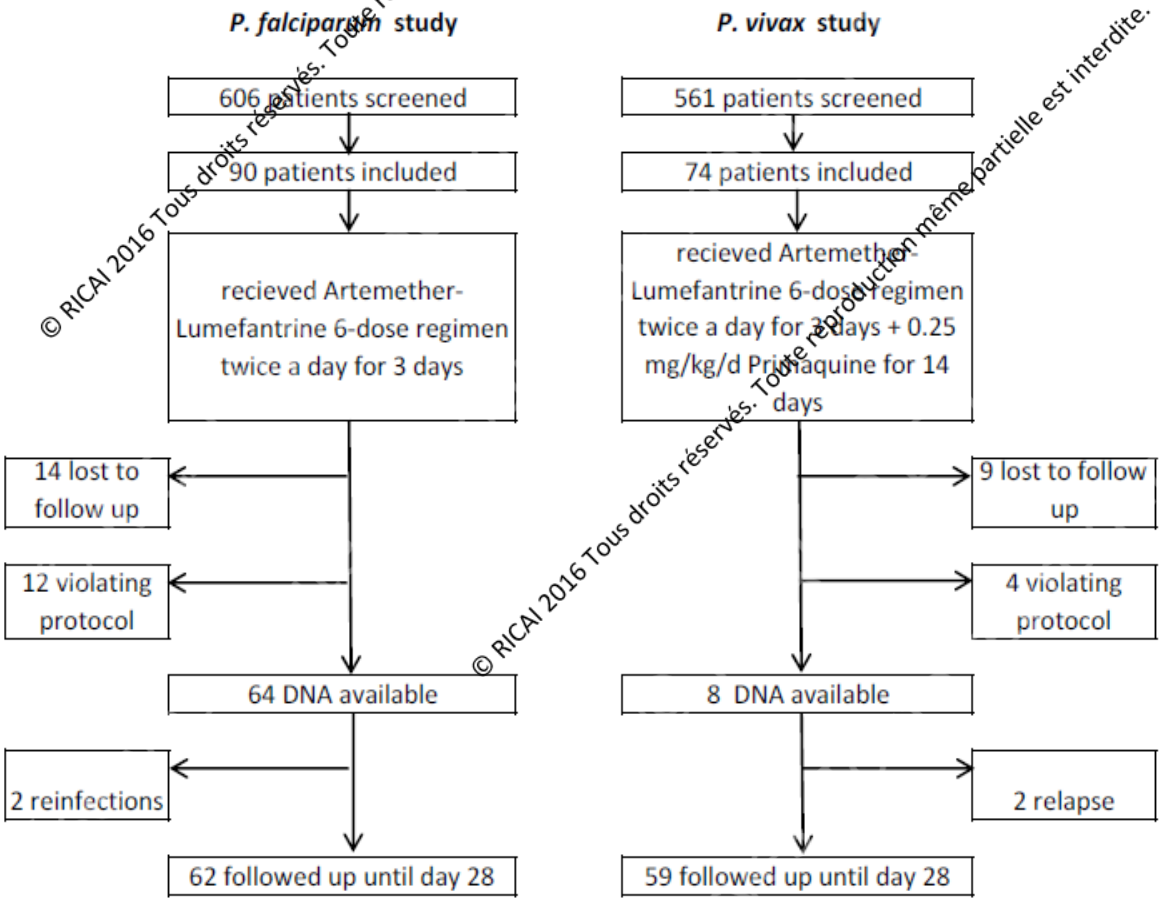
MALARIA JOURNAL

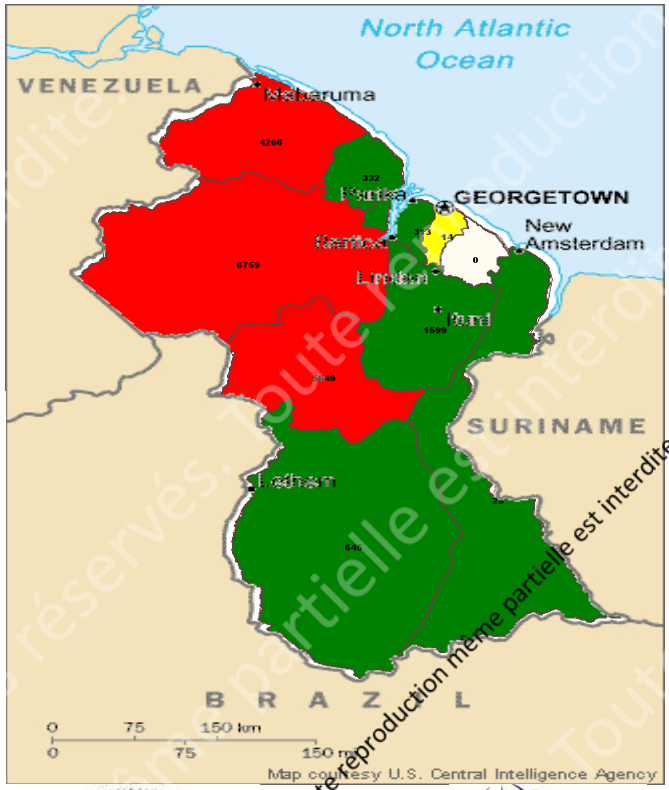
RESEARCH Open Access

Therapeutic efficacy of artemether-lumefantrine for *Plasmodium vivax* infections in a prospective study in Guyana

Daniel Eibach[1,2*], Nicolas Ceron[3], Karanchand Krishnalall[4], Keith Carter[5], Guillaume Bonnot[1], Anne-Lise Bienvenu[1] and Stéphane Picot[1]

Figure 1. Flow chart of the study procedure





Ethical Clearance by the Ethics Committee of the Ministry of Health of Guyana. Informed written consent was provided by all patients or their parents/guardians before inclusion in the study.

World Health Organization

GLOBAL TECHNICAL STRATEGY FOR MALARIA 2016–2030

VISION – A WORLD FREE OF MALARIA

GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

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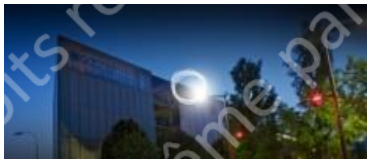

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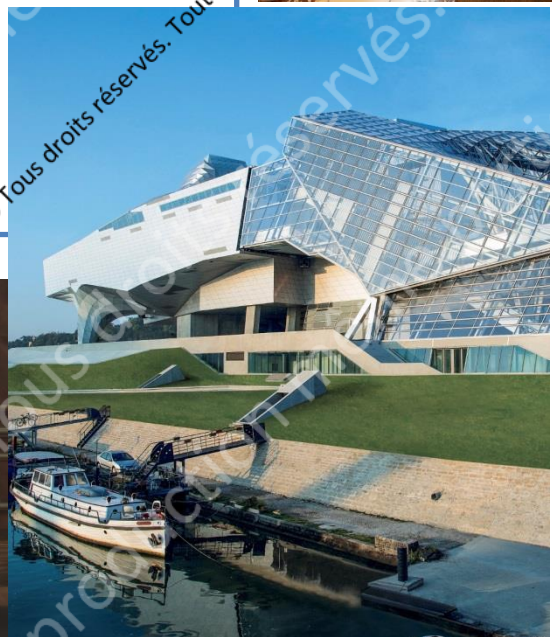
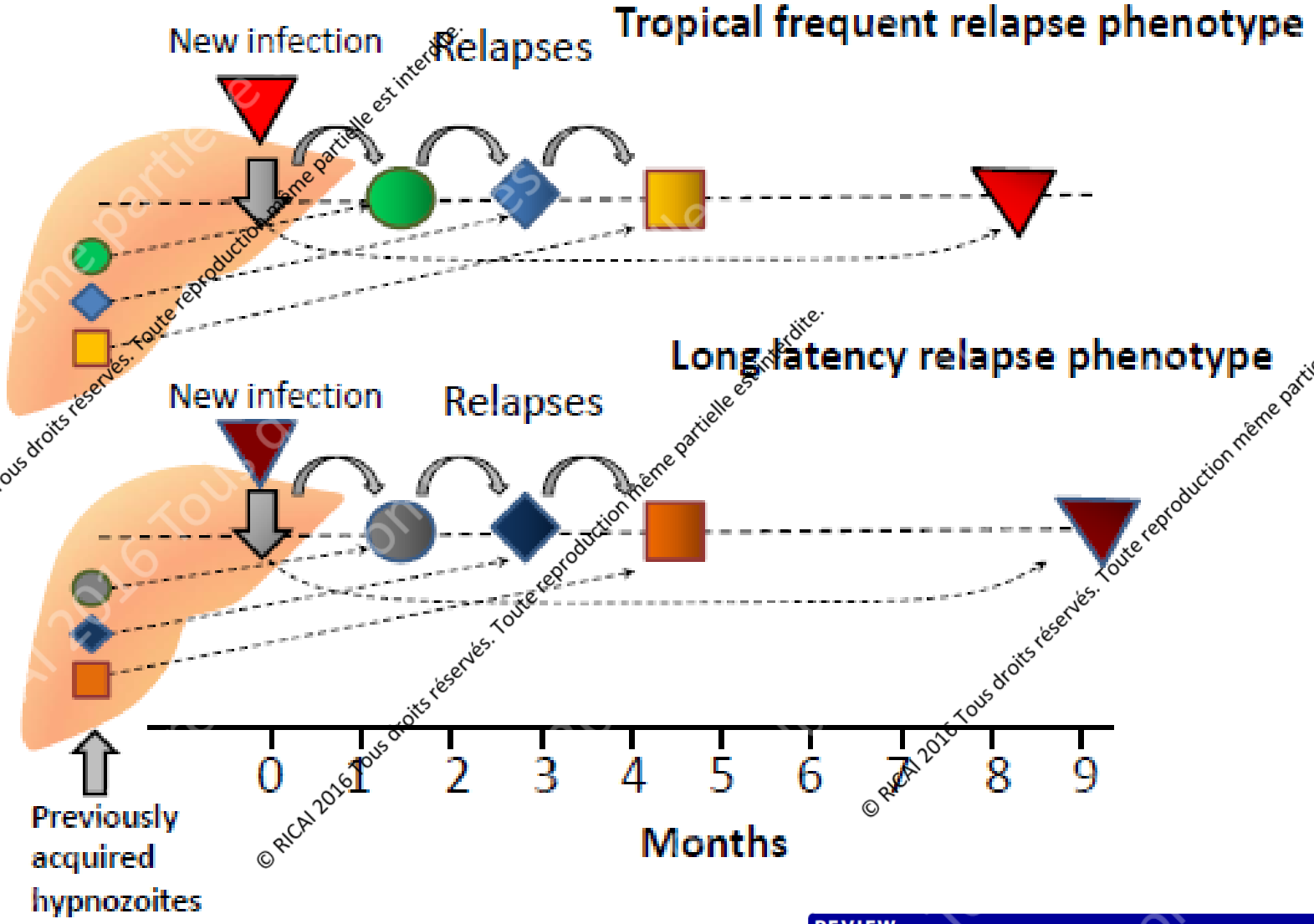
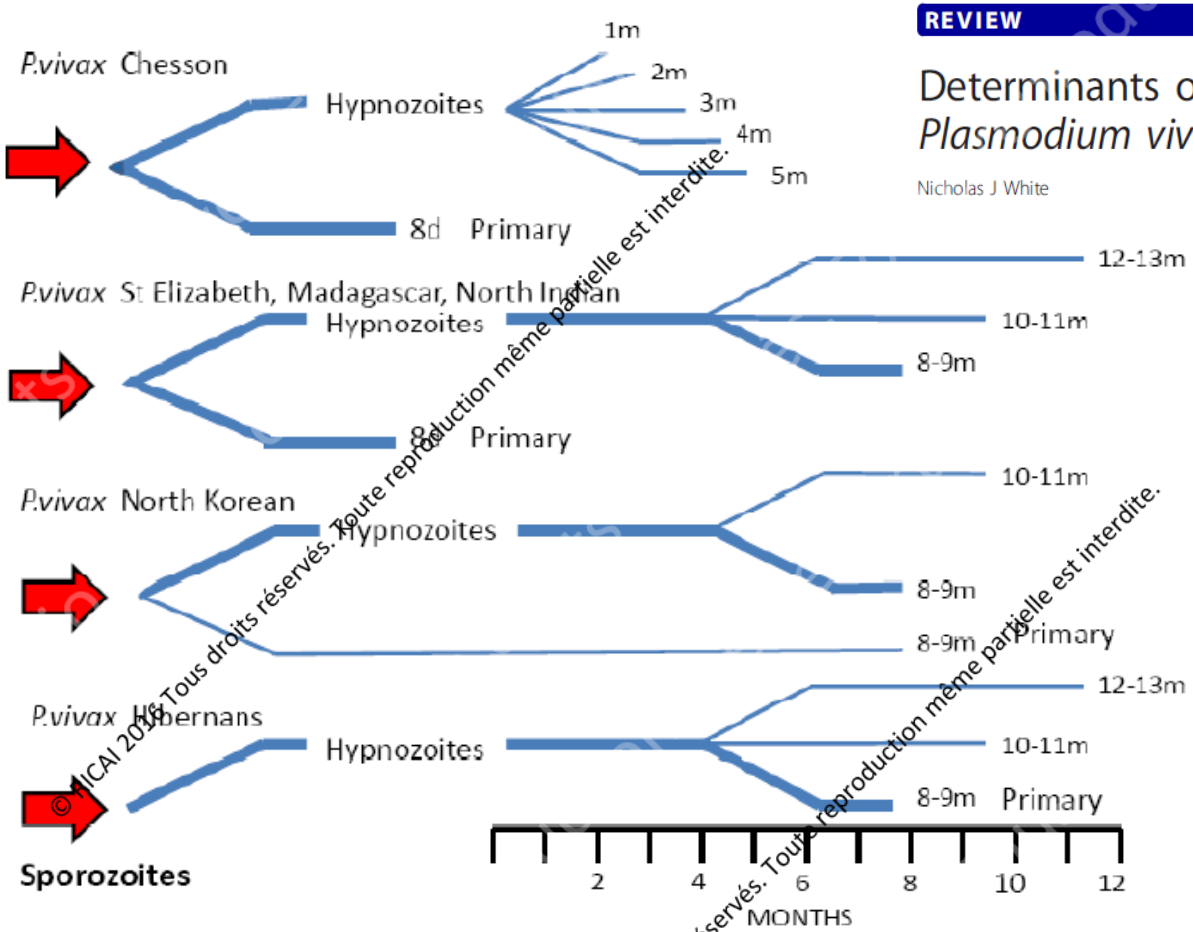




REVIEW

Determinants of relapse periodicity in *Plasmodium vivax* malaria

Nicholas J White



REVIEW

Determinants of relapse periodicity in *Plasmodium vivax* malaria

Nicholas J White

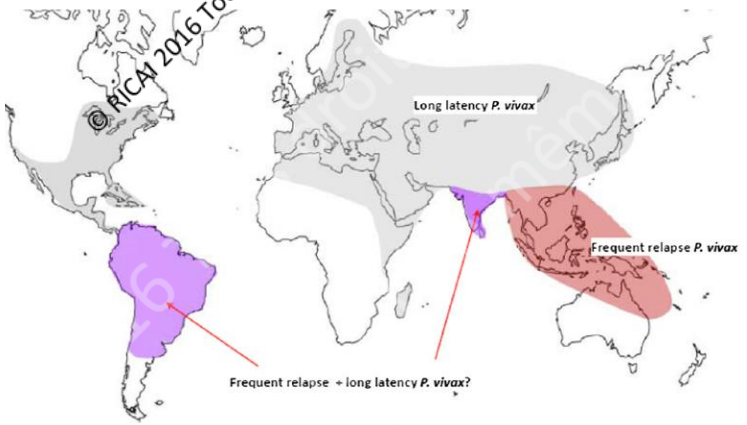


Figure 3 Approximate historical distribution of *P. vivax* phenotypes (White NJ 2011).

Plasmodium vivax malaria: A re-emerging threat for temperate climate zones?

Eskild Petersen [a,*], Carlo Severini [b], Stephane Picot [c,d]

Figure 3.4. Pharmacokinetics of artemisinins after a standard single oral dose

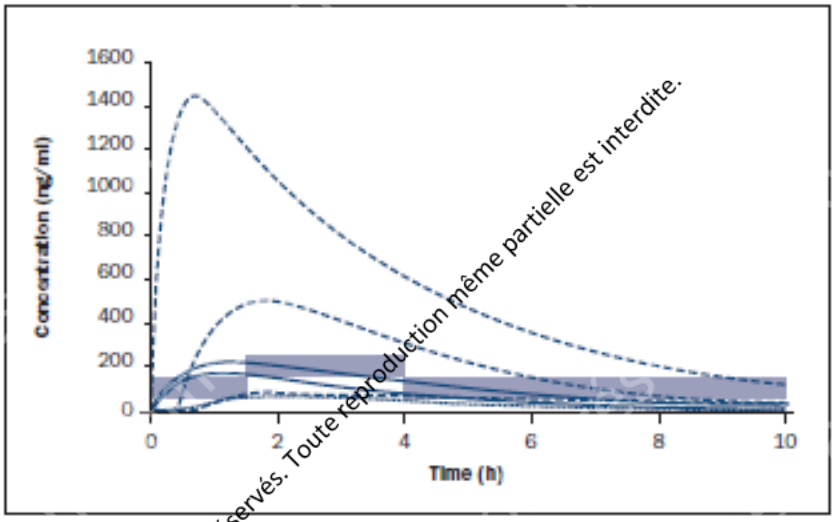


Figure 3.10. Pharmacokinetics of mefloquine after a standard oral treatment

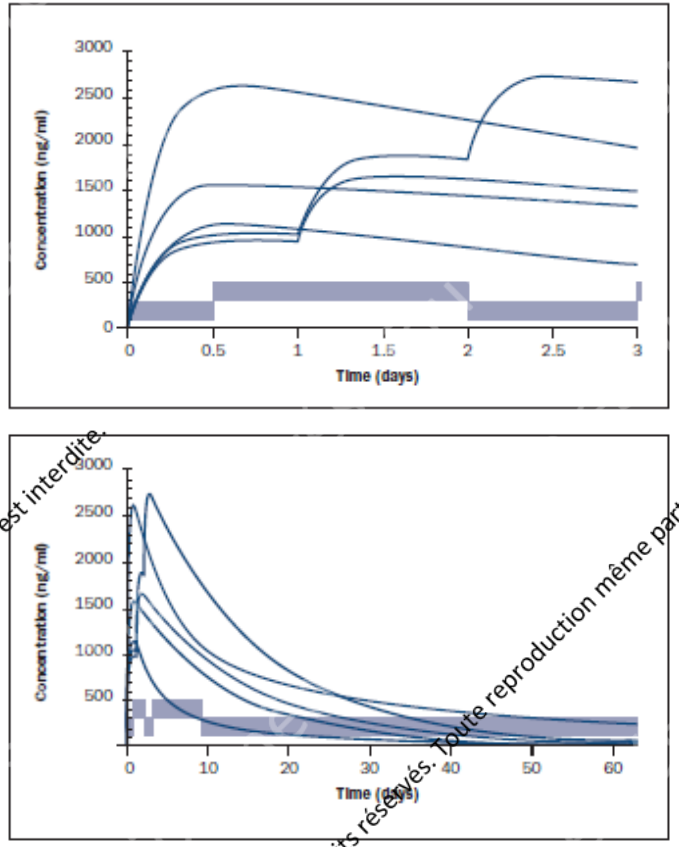


Figure 3.9. Pharmacokinetics of lumefantrine and desbutyl-lumefantrine after a standard oral treatment

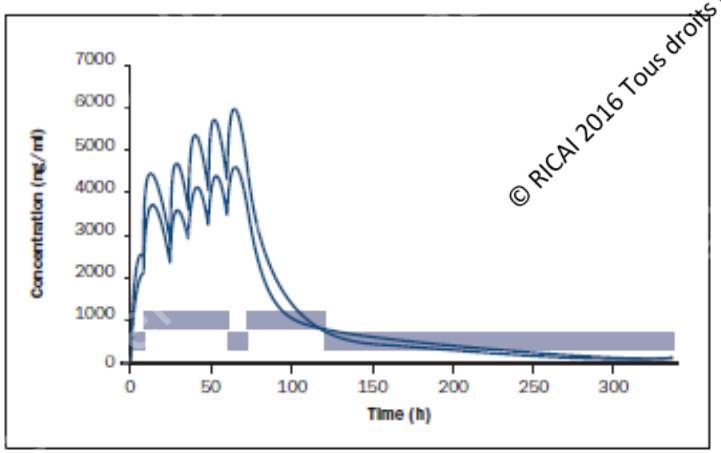


Figure 3.6. Pharmacokinetics of atovaquone after a standard oral treatment

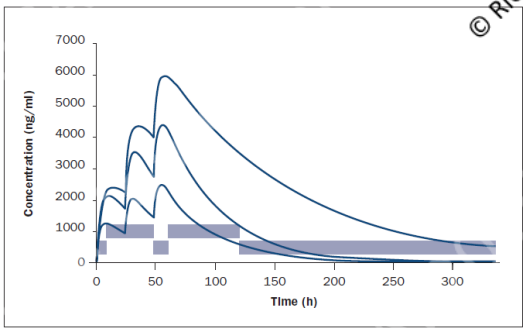


Figure 3.7. Pharmacokinetics of proguanil after a standard oral treatment

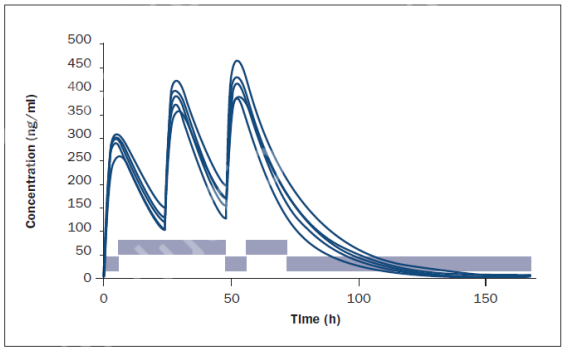
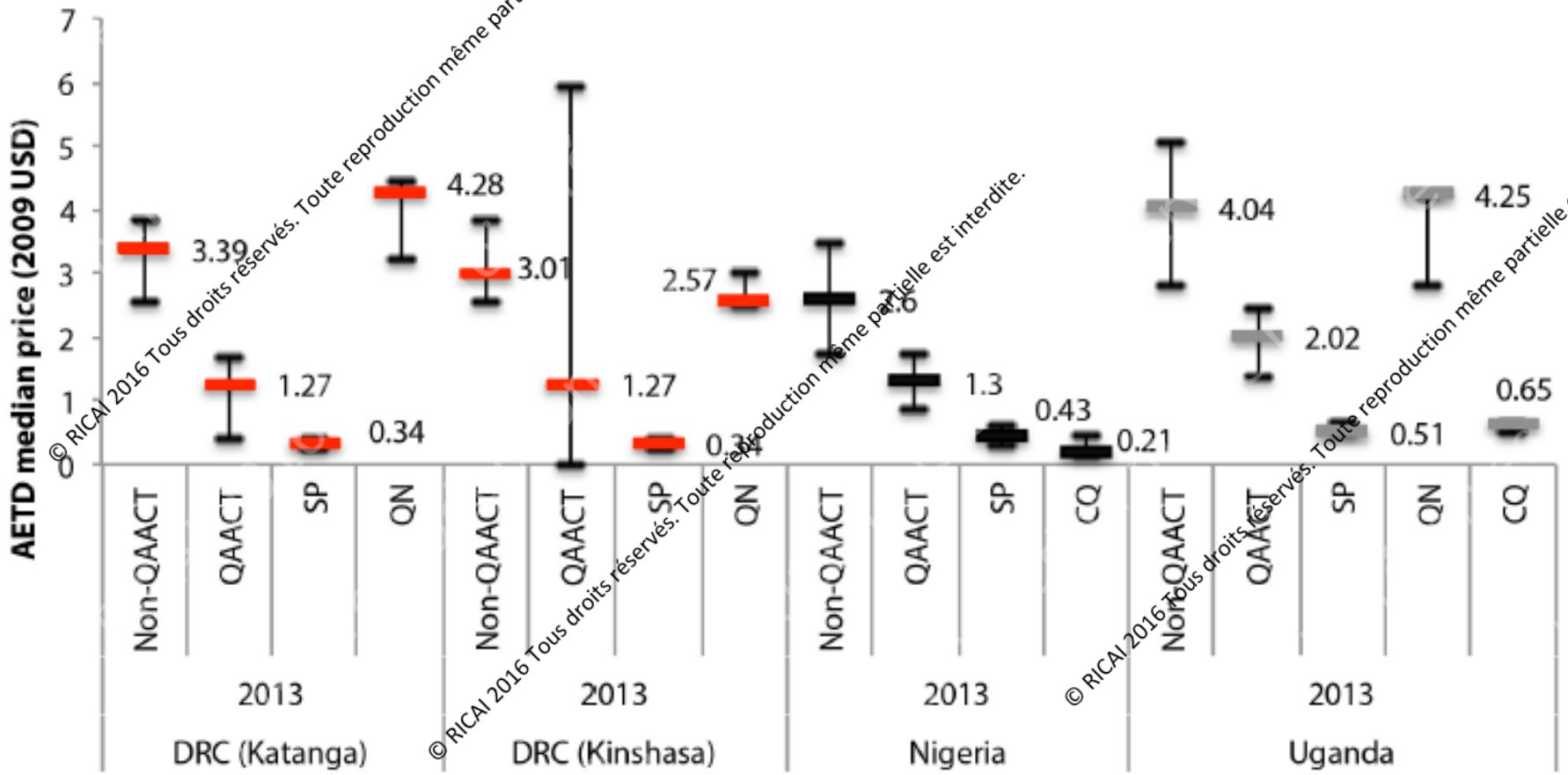
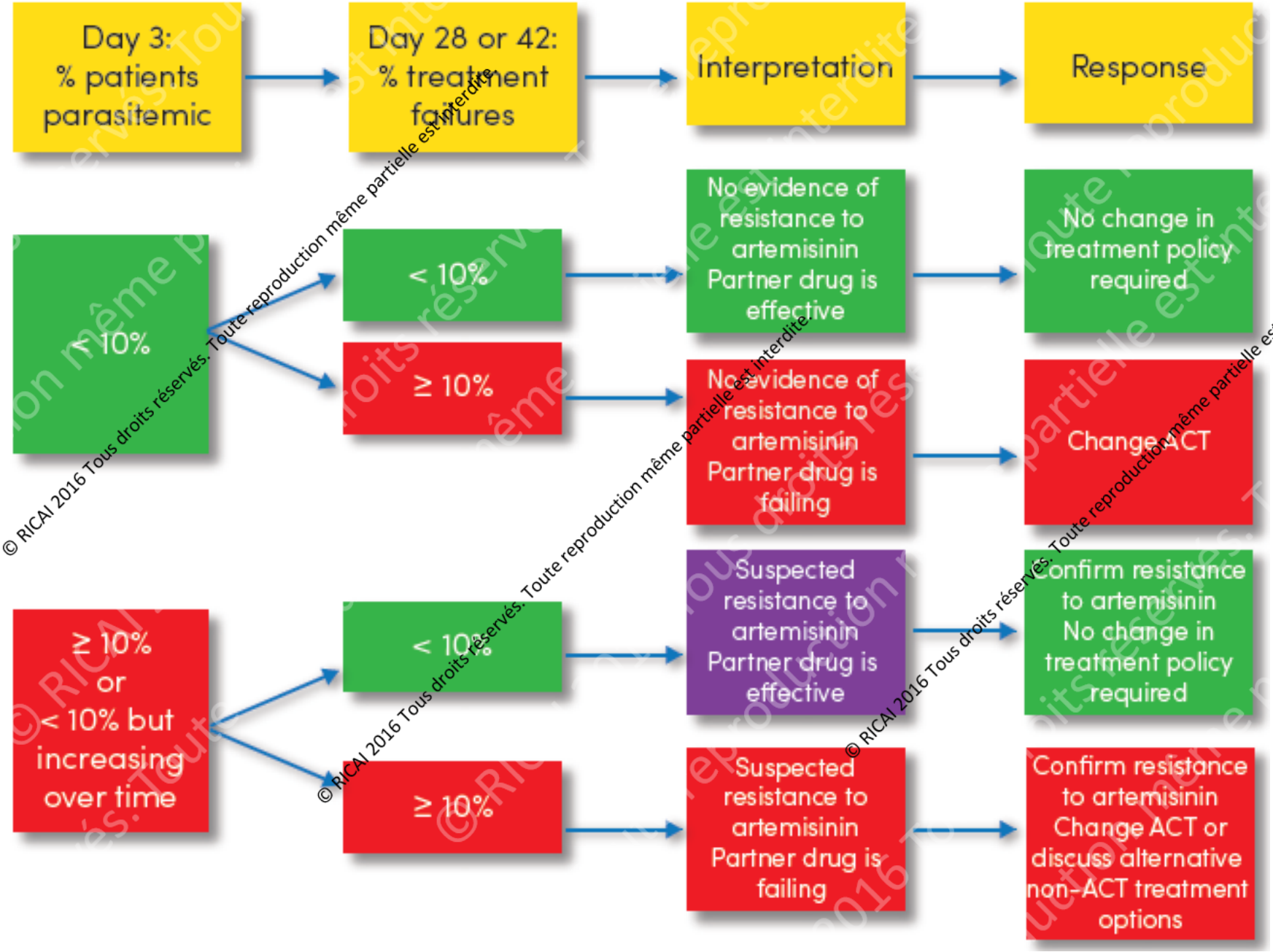


Figure 26. Price of QAACTs, non-QAACTs and non-oAMTs, AETD among outlets stocking at least one antimalarial at the time of survey in the private sector, 2013





Resistance to Artemisinin

ACTs available in Cambodia and Vietnam over 20 yrs

- 2002 Pailin -> AS-MQ day 28 failure rate : 14%
- 2004 Pailin -> AS-MQ day 42 failure rate : 21%
- …
- 2013 Oddar Meanchey -> DHA-PP day 63 FR : > 50%
- Many more…

Resistance: De novo emergence / subsequent spread

De novo emergence

- Rare : less than 10 times in 50 years for CQ
- Non-immune patient with high parasitemia & insufficient treatment
- New mutant parasite multiplication to produce transmissible densities of gametocytes (> 8 generations)

Subsequent spread

- Transmission to susceptible patient
- Windows of selection (low drug concentration)